Response to Office Action Mailed April 7, 2008

A. Claims In The Case

1-27, 29-32, 63, and 128 have been rejected. Claims 1, 18, 32, and 63 have been amended. Claims 2, 3, 4, 10, 15, and 128 have been canceled. Claims 1, 5-9, 11-14, 16-27, 29-32, and 63 are pending in the case.

B. The Claims Are Not Obvious Over The Cited Art Pursuant To 35 U.S.C. § 103(a)

Claims 1-19, 21, 23, 25, 27, 29, 30, 32, 63 and 128 stand rejected under to 35 U.S.C. §103(a) as being obvious over the teachings of U.S. Patent No. 4,927,676 to Williams et al. ("Williams") in view of U.S. Patent No. 6,582,391 to Mineau-Hanschke ("Mineau '391") and U.S. Patent No. 6,419,920 to Mineau-Hanschke ("Mineau '920"), and if necessary in view of U.S. Patent No. 5,034,265 to Hoffman et al. ("Hoffman '265") or U.S. Patent No. 6,033,582 to Lee et al. ("Lee") or U.S. Patent No. 5,055,316 to Hoffman et al. ("Hoffman '316").

Claims 1, 32, and 63 have been amended to include the feature:

> subjecting a bioresorbable polymeric substrate to a gas-plasma treatment, wherein subjecting the substrate to a gas-plasma treatment comprises exposing the substrate to a reactive gas, wherein the reactive gas comprises oxygen, and wherein the supplied energy during the gas-plasma treatment is between about 5 kJ and about 10 kJ.

Support for the amendment may be found at least in original claims 2, 3, 4, 10, and 15. Applicant submits that the prior art references, taken alone or in combination, appear to be silent on the combination of features set forth in the amended claims or any claims depending therefrom.

In order to reject a claim as obvious, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Warner et al.,* 379 F.2d 1011, 154 USPQ 173, 177-178 (CCPA 1967). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), MPEP § 2143.03.

Applicant's claims include, but are not limited to the feature of "subjecting a bioresorbable polymeric substrate to a gas-plasma treatment, wherein subjecting the substrate to a gas-plasma treatment comprises exposing the substrate to a reactive gas, wherein the reactive gas comprises oxygen."

With respect to the use of a gas plasma, the Office Action refers to Williams as "attaching endothelial cells to a substrate by treating the substrate with a gas-plasma. The Office Action further states that the references to Hoffman and Lee also cite gas plasma treatment conditions. Applicant submits, however, that none of these references teach or suggest a gas plasma treatment process in which the "supplied energy during the gas-plasma treatment is between about 5 kJ and about 10 kJ."

With respect to the energy supplied, Applicant's specification states:

> Duration of a gas-plasma treatment, together with RF power, may determine the energy delivered to the plasma chamber during treatment. In an embodiment, duration of the gas-plasma treatment may be greater than about 1 minute to less than about 5 minutes, between about 2 minutes and about 4 minutes, or about 3 minutes. In an embodiment, the RF power may range between about 25 watts and about 250 watts, between about 40 watts and about 100 watts, or about 60 watts. In some embodiments, treatment duration and RF power may be selected such that the product of power in watts and treatment duration in seconds is equal to a supplied energy between about 2 kJ and about 20 kJ, between about 5 kJ and

about 10 kJ, or about 7.5 kJ. For example, a three-minute treatment with a RF power of 100 watts delivers a supplied energy of

100 watts x 180 seconds = 18,000 J,

or 18 kJ, to the plasma chamber during treatment. In some embodiments, the RF power and/or phase may be varied during treatment.
(Specification, pg. 8, line 28 – pg. 9, line 10)

Applicant has determined that, unexpectedly, the power applied during a plasma treatment, as defined above, has a significant effect on the formation of radical groups on the surface of the substrate. For example, Applicant's specification states:

Gas-plasma treatment may induce formation of free radicals on a substrate. In an embodiment, gas-plasma treatment with a reactive gas that includes oxygen may induce formation of oxide free radicals on a substrate. As shown below, parameters chosen for a gas-plasma treatment may influence relative density of free radicals formed on the substrate.

Electron spectroscopy for chemical analysis ("ESCA") data from three-dimensional plug-shaped DL-PLA implants (5 mm diameter x 2 mm thick) were used to compare mass concentration percentages corresponding to carbon atoms in various bonding configurations, including C=O, C-O, C-C, and C-O-O bonds, where applicable. Table 1 shows the percentages of C=O, C-O, and C-C bonds in an untreated substrate. Tables 2-4 show data from substrates subjected to gas-plasma treatment with an RF setting of 100 watts, and RF frequency of 10-11 MHz, a vacuum of 100-200 mtorr., using oxygen as the reactive gas. Table 2 shows percentages of C=O, C-O, C-C, and C-O-O bonds on a substrate following a 1 minute gas-plasma treatment with a RF power of 100 watts (supplied energy = 6 kJ) . Table 3 shows percentages of C=O, C-O, C-C, and C-O-O bonds on a substrate following a 3 minute gas-plasma treatment with a RF power of 40 watts (supplied energy = 7.2 kJ). Table 4 shows percentages of C=O, C-O, C-C, and C-O-O bonds on a substrate following a 3 minute gas-plasma treatment with a RF power of 100 watts (supplied energy = 18 kJ).

TABLE 1: Untreated

Peak	Position (eV)	Mass Concentration %
C=O	287.020	33.35
C-O	284.919	33.33
C-C	282.946	33.32

TABLE 2: Gas-plasma treated: 1 minute, 100 watts

Peak	Position (eV)	Mass Concentration %
C=O	282.843	31.47
C-O	284.748	34.59
C-C	286.851	30.45
C-O-O	287.800	3.49

TABLE 3: Gas-plasma treated: 3 minutes, 40 watts

Peak	Position (eV)	Mass Concentration %
C=O	286.941	39.12
C-C	284.802	31.77
C-C	282.907	22.70
C-O-O	288.797	6.41

TABLE 4: Gas-plasma treated 3 minutes, 100 watts

Peak	Position (eV)	Mass Concentration %
C=O	282.847	37.88
C-O	284.712	32.48
C-C	286.946	29.64

Data from the untreated substrate in Table 1 suggest that C=O, C-O, and C-C bonds are present in approximately equal numbers, with each bond type corresponding to approximately one-third of the carbon-containing surface bonds. Data from Table 2 for a substrate treated at a RF power of 100 watts for 1 minute suggest that gas-plasma treatment induced the formation of oxide radicals, with relative occurrences of C=O, C-O, C-C, and C-O-O bonds measured as 31.47%, 34.59%, 30.45%, and 3.49%, respectively. Data from Table 3 for a substrate treated at a RF power of 40 watts for 3 minutes suggest that gas-plasma treatment induced an even greater formation of oxide radicals, with relative occurrences of C=O, C-O, C-C, and C-O-O bonds measured as 39.12%, 31.77%, 22.70%, and 6.41%, respectively. Thus, the relative percentage of oxide radicals is almost twice as high for a 40 watt, 3 minute gas-plasma treatment than for a 100 watt, 1 minute gas-plasma treatment. Data from Table 4, with relative occurrences of C=O, C-O, and C-C bonds measured as 31.47%, 34.59%, and 30.45%, respectively, suggest that treatment at a RF power of 100 watts for 3 minutes does not promote formation of oxide radicals.
(Specification, pg. 10, line 1 – pg. 11, line 17)

The formation of radicals on the surface of an implant is known to have a number of beneficial effects. For example, free radicals on implant surfaces may simulate in vivo vascular injury, thereby promoting endothelial cell activation and induction of blood vessel formation, or angiogenesis. Applicant has shown that bioresorbable polymeric substrates exposed to a reactive gas, wherein the reactive gas comprises oxygen, and wherein the supplied energy during the gas-plasma treatment is between about 5 kJ and about 10 kJ creates substrates having the unexpected benefit of additional radical formation on the surface. In addition, Applicant has shown that at supplied energies significantly above this range (for example, as shown in Table 4), little or no radical formation is seen.

Applicant has further shown that such treatments also produce another unexpected benefit. During testing the "living cells coupled to the treated substrate produce more of one or more cellular products than living cells coupled to an untreated substrate." That is, when a living cell is coupled to the treated substrate, the amount of cellular products produced by each individual cell is greater than the amount of cellular product produced by an individual cell when coupled to the same substrate. This benefit was also unexpected and unknown prior to Applicant's discovery of this effect.

Applicant submits that the benefits and unexpected treatment of bioresorbable polymers with a gas plasma at supplied energy of between about 5 kJ and about 10 kJ is neither taught nor suggested by the cited art. For example, Williams teaches:

> Plasma generation for surface modification in accordance with the present invention may be carried out with a wide range of power settings, radio frequencies, durations of exposure, temperatures, and gas pressures. Ranges for these parameters which provide advantageous results are measured DC or AC power density levels of from 0.001 to 400 watts per cubic centimeter, oscillation frequencies up to 100 megahertz, 2 seconds to 12 hours, 0° to 200° C., and 0.01 to 100 torr. Preferred ranges for these parameters are 0.01 to 200 watts per cubic centimeter, 5 to 30 megahertz, 5 seconds to 120 minutes, 10°-50° C., and 0.01 to

> 20 torr. Gas flow rates may vary from stagnant conditions to several volume replacements per second.

Although Williams teaches a wide range that includes the energy ranges of Applicant's claims, Applicant submits that one of ordinary skill in the art would not recognize the importance of maintaining a supplied energy range of between about 5 kJ and about 10 kJ. In fact, Williams does not appear to teach or suggest any conditions for the use of an plasma that comprises oxygen. The examples of Williams appear to describe the formation of ammonia based plasma that do not appear to include oxygen. As such, Applicant submits that "subjecting a bioresorbable polymeric substrate to a gas-plasma treatment, wherein subjecting the substrate to a gas-plasma treatment comprises exposing the substrate to a reactive gas, wherein the reactive gas comprises oxygen, and wherein the supplied energy during the gas-plasma treatment is between about 5 kJ and about 10 kJ" is not taught or suggested by Williams, nor would it be obvious from the teachings of Williams. For at least these reasons, Applicant submits that independent claims 1, 32, and 63 are patentable over the combination of references cited.

Applicant notes that Lee appears to teach subjecting the substrate to a gas-plasma treatment that includes exposing the substrate to a reactive gas, wherein the reactive gas comprises oxygen. For at least the same reasons cited above for Williams, Applicant submits that it would not be obvious to control the supplied energy to be in the range of between about 5 kJ to about 10 kJ. Furthermore, Lee teaches the use of an oxygen containing plasma, but at supplied energy that is higher than 10 kJ. Specifically, Lee states:

> For this example, poly(L-lactic acid) [PLLA] suture material (0.05 mm diameter) was subjected to a helium and an argon plasma with a small amount of water vapor. PLLA suture material was placed in a plasma reaction chamber with approximately 15-mL reservoir of distilled water to generate the reactive species. The chamber was evacuated to $5x10^{-5}$ Torr, Ar was introduced at a flow rate of approximately 50 sccm, and a chamber pressure of 0.050 Torr was established. The RF power source was switched to the power mode and set to 80 watts. Reactive etching continued for a total of 75 minutes at an operating temperature of

> approximately 25° C. (room temperature), at which point the power was turned off and the chamber was evacuated to $5x10^{-6}$ Torr. The chamber was allowed to equilibrate to standard atmospheric conditions and the etched PLLA material was removed and was subsequently examined with SEM. In a second experiment, identical procedures are employed to etch a second sample of PLLA suture material except that helium (He) is used in the plasma rather than Ar.
> (Lee, Col. 21, line 66 – Col. 2, line 17)

Lee appears to teach that the treatment of PLLA is performed using a power setting of 80 watts for a time of 75 minutes. This would represent a supplied energy of:

80 watts X 4500 seconds = 360,000 J (36kJ)

Such an energy is significantly greater than Applicant's claimed upper range of 10 kJ. As noted above, treatment at supplied energies above 10kJ significantly reduces the amount of radicals formed on the surface and reduces the effectiveness of an implant made at the higher energies. For at least these reasons, Applicant submits that independent claims 1, 32, and 63 are patentable over the combination of references cited.

C. Summary

Based on the above, Applicant submits that all claims are now in condition for allowance. Favorable reconsideration is respectfully requested.

Applicant respectfully requests a three-month extension of time to respond to the Office Action dated April 7, 2008. A fee authorization form in the amount of $555.00 is enclosed for the extension of time fee. If any further extension of time is required, Applicant hereby requests the appropriate extension of time. If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Meyertons, Hood, Kivlin, Kowert & Goetzel, P.C. Deposit Account Number 50-1505/5660-00503/EBM

Respectfully submitted,

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